Making Sense of the Perchlorate Action Level Debate

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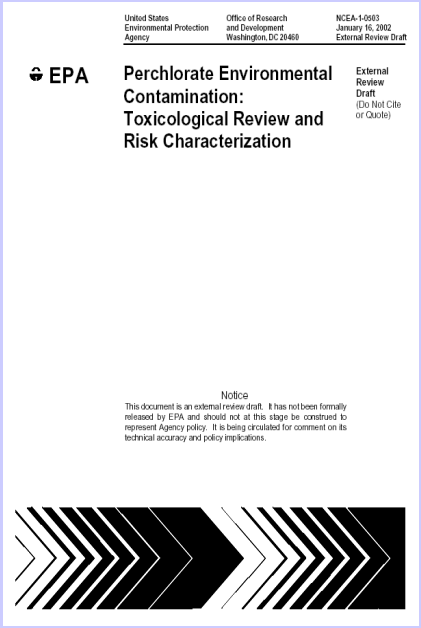
Perchlorate Exposure

Is perchlorate exposure a public health crisis?

EPA Risk Assessment appears complex, but boils down to this:



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EPA

Perchlorate Environmental Contamination: Toxicological Review and Risk Characterization

External Review Draft (Do Not Cite or Quote)

Notice

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- ✓ **Rat study suggests potential for neurodevelopmental harm**
- ✓ **"Critical effect" in humans is *iodine uptake inhibition***
- ✓ **Composite uncertainty factor = 300**

Each line of this argument is scientifically incorrect

- **Rat study…**
  - **Had limited value if performed properly**
  - **Data are useless due to lab errors**
- **Iodine uptake inhibition is mundane and normal, not an adverse effect**
- **A composite uncertainty factor of 300 is scientifically unjustified**

How can we show this?

- **Show how lab errors occurred in rat brain morphometry study**
- **Show that predictions from risk assessment are inconsistent with human data**
- **Show that potential iodine uptake inhibition from normal diet greatly exceeds that from perchlorate**

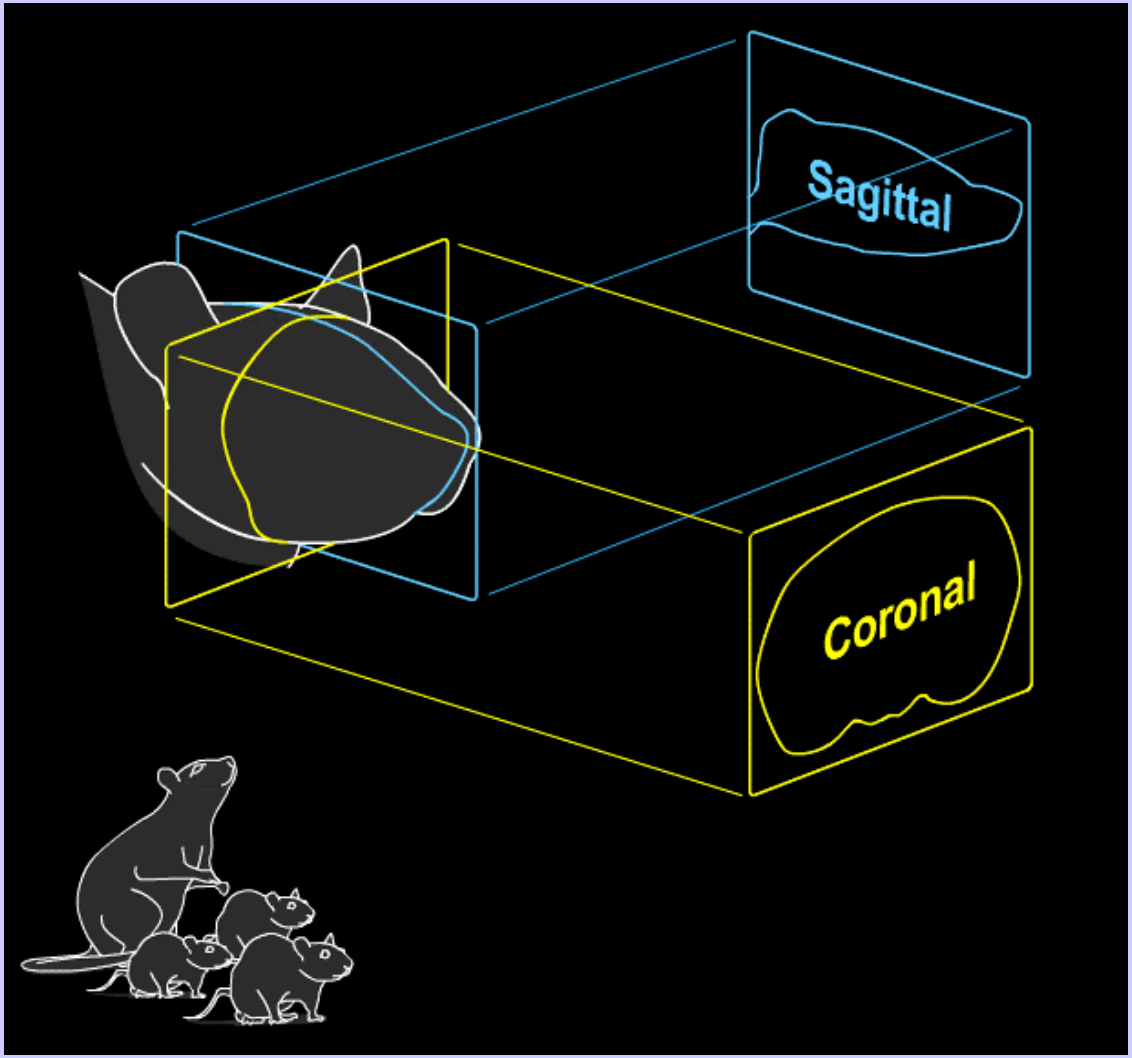
Rat Brain Morphometry Study

- **In the manner it was conducted, the rat brain morphometry study yields useless data, here is why:**
  - **The rat brains were cut incorrectly**
  - **A substandard and crude means of measuring effects was used**
    - **No sensitivity or specificity in data**
    - **More sensitive effects were not observed**

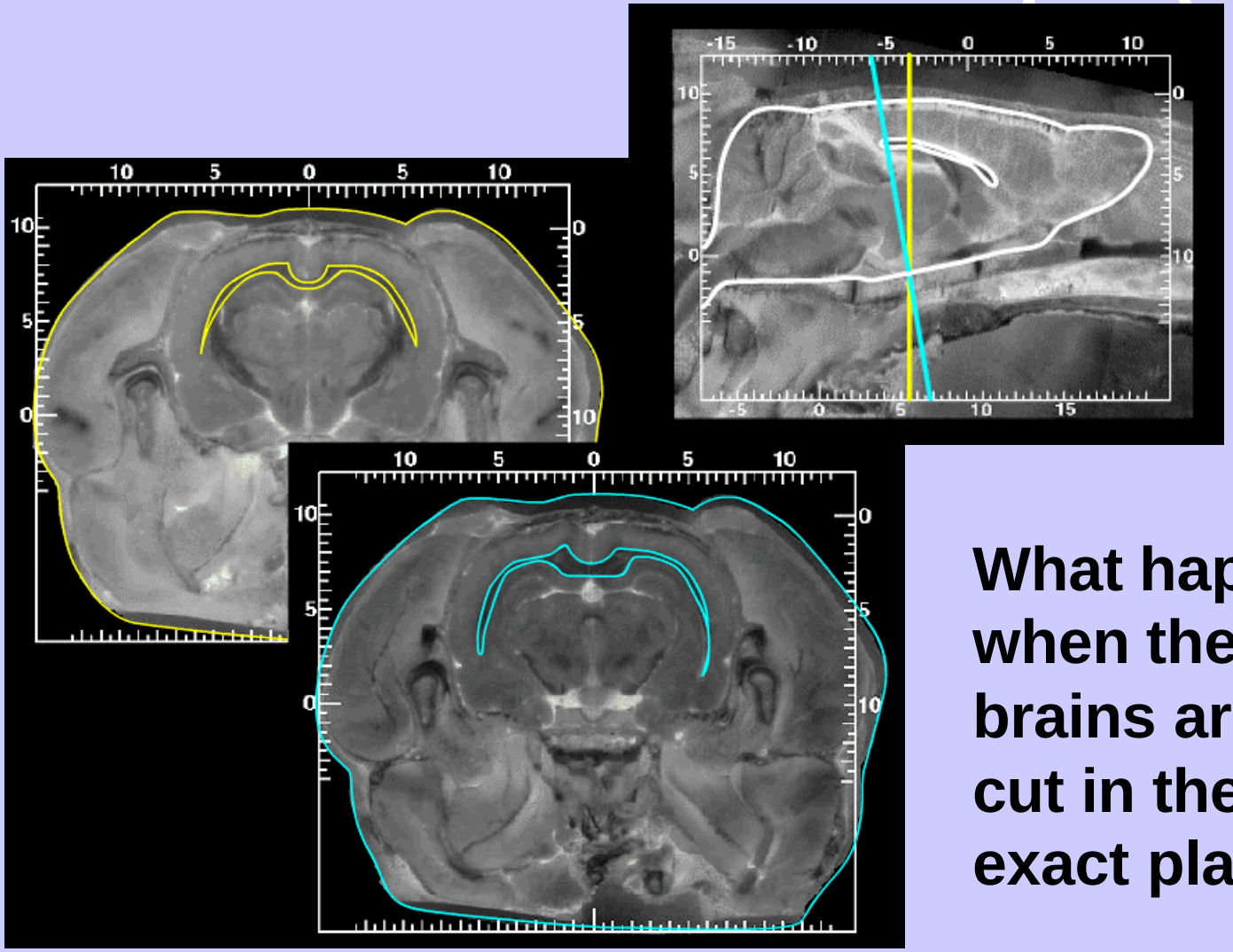
Dr. Douglas Wahlsten

- **The next several slides show work conducted by Dr. Wahlsten**
  - **Professor Emeritus, Dept of Psychology and Centre for Neuroscience, University of Alberta**
  - **Over 30 years of research on rodent brain anatomy, neurodevelopment, and animal behavior; reviewed papers for 42 peer reviewed journals; published in 34+ peer reviewed journals**
  - **A particular focus of his research is the development of the corpus callosum and its effect on behavior**

Different planes to cut brains



Brain structures were measured by their thickness (e.g. corpus callosum)



What happens when the brains are not cut in the same exact place?

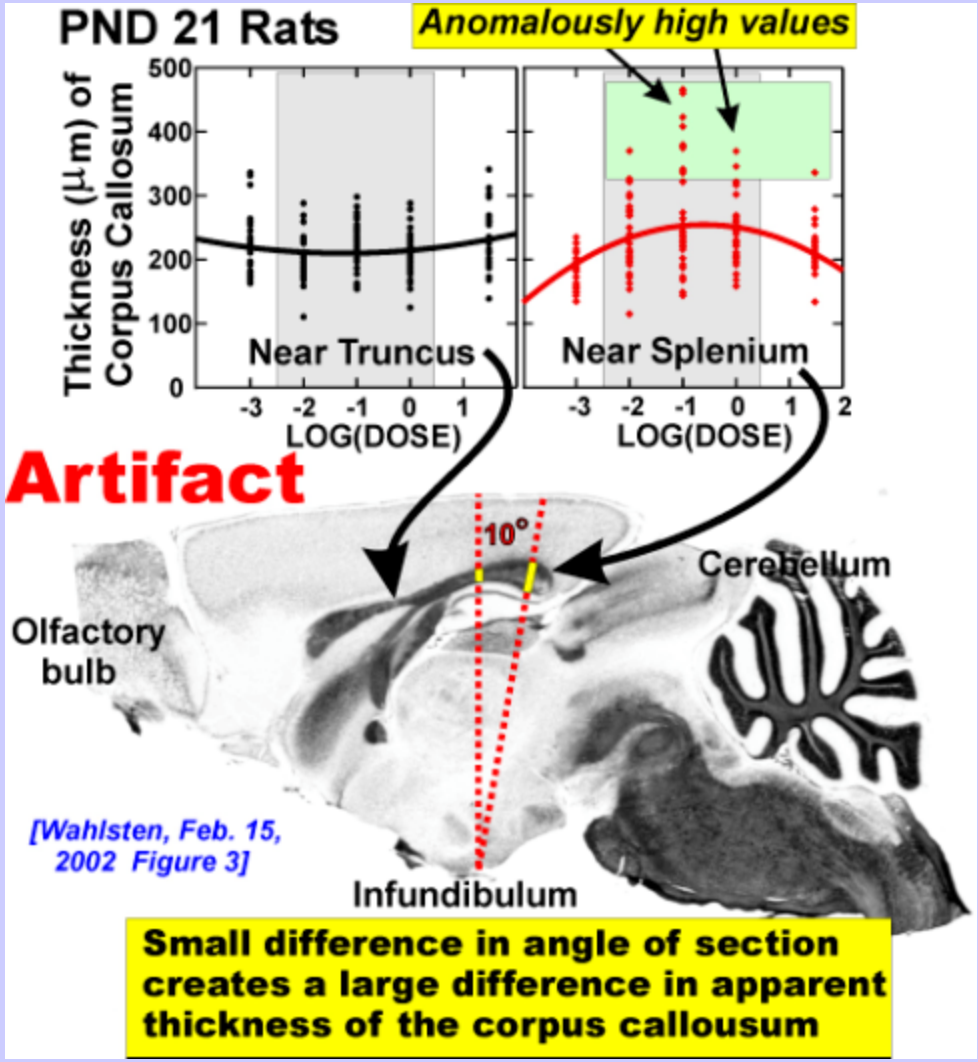
PND 21 Rats

RED CURVE

- Inverse U-shaped dose-response curve is the first sign of trouble
- Outliers are in the intermediate doses
- Artifacts of lab errors

BLACK CURVE

- Brain slices measured at truncus



Can information from human exposure tell us what is safe?

- **Use as a medication**
- **Clinical trials**
- **Comparative exposure assessment**

Pharmacologic experience with perchlorate

- **More than 50 years of experience**
- **Perchlorate's mechanism of action—*iodine uptake inhibition*– has been known for decades**
- **Safe and effective drug for the R_x thyrotoxicosis**
  - **Gram doses (more than 100,00 times higher)**
  - **It is not the drug of choice. Why?**
    - ✓ **Short lived and weak**
    - ✓ **Needs to be taken several times a day**

Can information from human exposure tell us what is safe?

- **Use as a medication**
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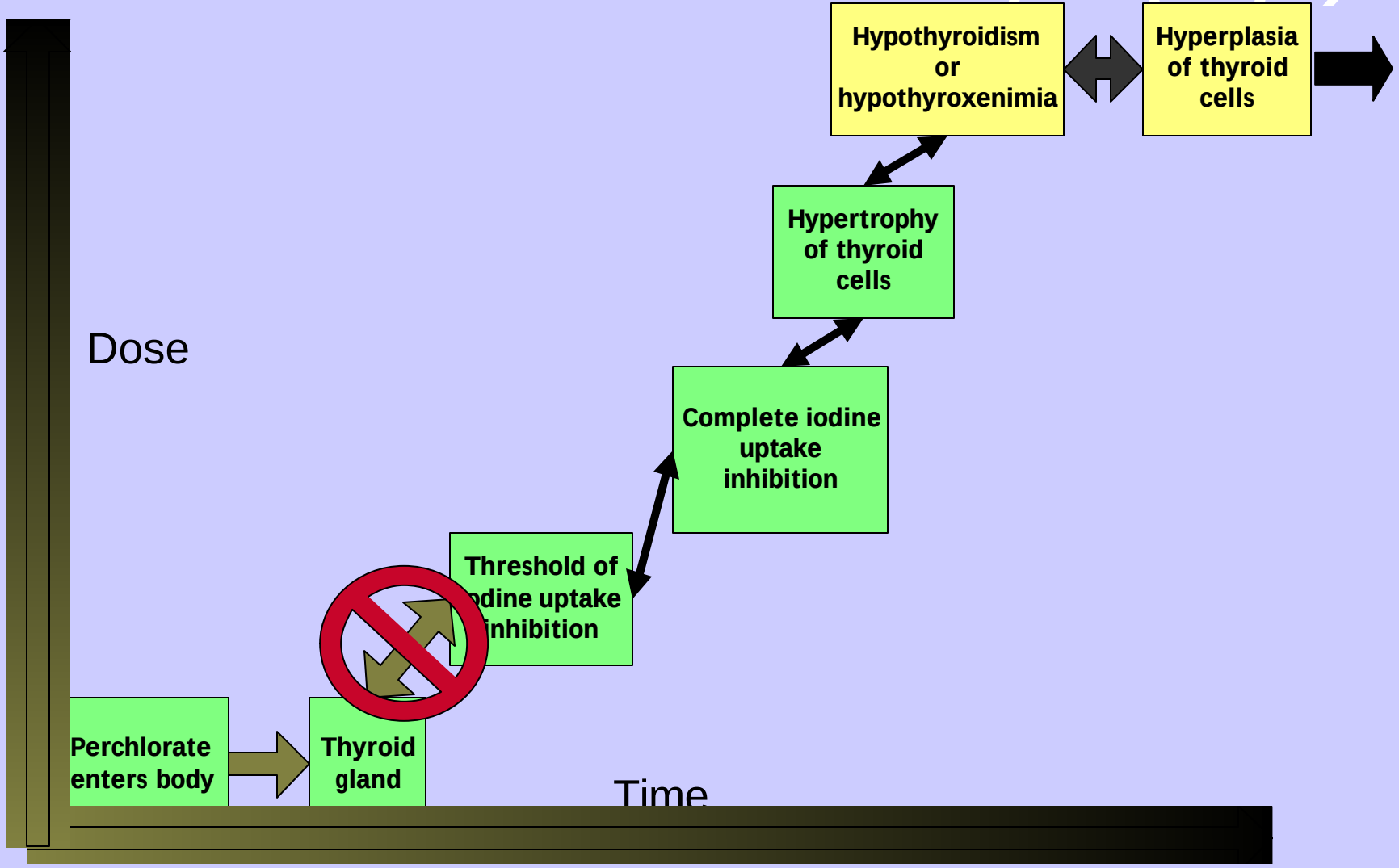
- **Comparative exposure assessment**

Cascade of events leading to an adverse effect



The Greer et al., 2002 Study

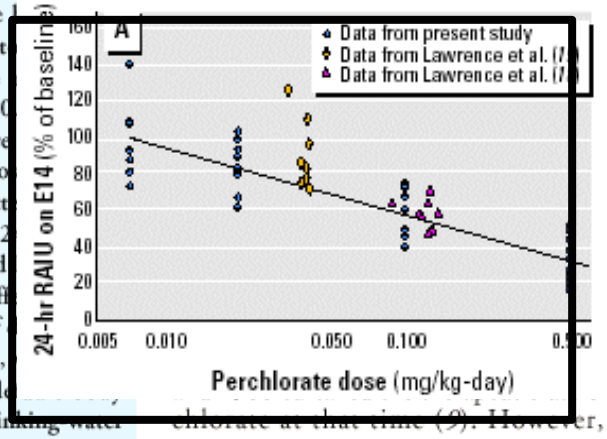
Health Effects Assessment for Environmental Perchlorate Contamination: The Dose Response for Inhibition of Thyroidal Radioiodine Uptake in Humans

Monte A. Greer,[1] Gay Goodman,[2] Richard C. Pleus,[2] and Susan E. Greer[1]

[1]Oregon Health & Science University, Portland, Oregon, USA; [2]Intertox, Inc., Seattle, Washington, USA

Application of a sensitive new detection method has revealed widespread perchlorate contamination of groundwater in the southwestern United States, typically at 0.005–0.020 mg/L (5–20 ppb). Perchlorate is a competitive inhibitor of the process by which iodide is actively t from the bloodstream into the thyroid. This inhibitory action of perchlorate is the l pharmaceutical use (in the treatment of hyperthyroidism) as well as its potential t establish the dose response in humans for perchlorate inhibition of thyroidal iodide any short-term effects on thyroid hormones, we gave perchlorate in drinking water at 0 0.1, or 0.5 mg/kg-day to 37 male and female volunteers for 14 days. In 24 subjects we 8- and 24-hr measurements of thyroidal ^{123}I uptake (RAIU) before exposure, on expo (E2) and 14 (E14), and 15 days postexposure (P15). In another 13 subjects we omitt studies and the 8-hr P15 study. We observed a strong correlation between the 8- and 2 over all dose groups and measurement days. We found no difference between E2 and inhibition of RAIU produced by a given perchlorate dose. We also found no sex diff both E2 and E14, the dose response was a negative linear function of the logarithm of on the dose response for inhibition of the 8- and 24-hr RAIU on E14 in all subjects, estimates of the true no-effect level: 5.2 and 6.4 µg/kg-day, respectively. Given d weight and exposure assumptions, these doses would be ingested by an adult if the dri supply contained perchlorate at concentrations of approximately 180 and 220 µg/L (ppb), respectively. On P15, RAIU was not significantly different from baseline. In 24 subjects we measured serum levels of thyroxine (total and free), triiodothyronine, and thyrotropin in blood sampled 16 times throughout the study. Only the 0.5 mg/kg-day dose group showed any effect on serum hormones: a slight downward trend in thyrotrop exposure, with recovery by P15. *Key words:* c sodium-iodide symporter, thyroid. *Enviro* 14 August 2002]
http://ehpnet1.niehs.nih.gov/docs/2002/110p92

any potentially adverse effect of perchlorate and is also the basis for its major current and former pharmaceutical usages.



decades later, physicians reported treating thyrotoxicosis successfully with lower maintenance doses of potassium perchlorate

Collaborative work with Drs. Monte Greer, Gay Goodman, and Ms. Susan Greer

Environ Health Perspect 110:927–937 (2002).

Greer et al., 2002 clinical trial

Greer *et al.*, 2002 clinical trial was constructed to take advantage of the pharmacology of perchlorate

- **At very high doses perchlorate shuts down overproduction of thyroid hormones**
- **At low doses, perchlorate does nothing**
- **At what dose does perchlorate begin to inhibit iodine uptake?**
  - **That level is a *no-effect level***
  - **A *no-effect level* is inherently protective of everyone**
  - **If nothing happens, nothing bad can happen**

Results of Greer et al., 2002

Doses (mg/kg-day, 14 days)	DWEL (ppb)	Were side effects observed?	Did effects in rats appear in humans? (Acute ¯T3, T4 or ? TSH)	*IUI* (rounded, % baseline)
0.5	17,500	No	No	67
0.1	3,500	No	No	44
.02	700	No	No	17
.007	245	No	No	0

Threshold for iodide uptake inhibition ¡ 180-220 ppb

- 200 times greater than EPA proposed RfD/DWEL
- Response to criticisms we have heard:
  - Sample was too small:
    - N = 37 consistent with typical clinical trial, and low variation across subjects
  - Exposure duration was too short:
    - Short duration was sufficient to test the hypothesis that acute TH changes observed in rats also occur in humans
    - Duration is not relevant for estimating no-effect threshold
  - No sensitive subpopulations were tested:
    - No differences between adult men and women
    - Testing pregnant women is unethical
    - Mechanism of action is the same for pregnant women

What about sensitive subpopulations?

- **Uncertainty or safety factors are not scientifically justified**
  - ***Iodine uptake inhibition* is fully reversible**
  - ***Iodine uptake inhibition* is several steps removed from true adverse effect; a large safety factor is already built in**
- **Epi studies with high actual perchlorate measurements consistently show no effects on thyroid hormones**
- **Epi studies that claim to show an effect did not actually measure perchlorate exposure**
  - **What did they really measure?**
  - **Control for multiple confounders is very hard but essential before inferring a real effect**

What else do we know about perchlorate?

- **Not a carcinogen**
- **Not a mutagen**
- **Not immunotoxic**
- **Not a reproductive toxin**
- **Does not accumulate in body**
- **Excreted in hours (short $T_{1/2}$)**

What do EPA and CA OEHHA imply?

EPA and CA OEHHA imply that *iodide uptake inhibition* is an adverse effect

- **This is odd because *iodide uptake inhibition* is a mundane and commonplace occurrence**
- **A wide range of factors cause *iodide uptake inhibition*, including stress, time of day, and diet**
- **We took advantage of old pharmacological knowledge to estimate how much *iodide uptake inhibition* occurs everyday through the diet**

Can information from human exposure tell us what is safe?

- **Use as a medication**
- **Clinical trials**
- **Comparative exposure assessment**

How much iodide uptake inhibition is normal?

- Comparative exposure assessment provides a reality check on the risk assessment
- Collaborative work with Richard Belzer, Gretchen Bruce, and Michael Peterson
- Scheduled for publication in 2003 by Kluwer (NATO Science Series)

Nitrate MCL and Perchlorate RfD/DWELs differ by 10,000x

- **Nitrate MCL = 10 ppm = 10,000 ppb**
  - **Based on methemoglobinemia**
- **Perchlorate RfD/DWEL = 1 ppb**
  - **Based on *iodide uptake inhibition***

Nitrate inhibits iodine uptake
Perchlorate inhibits iodine uptake

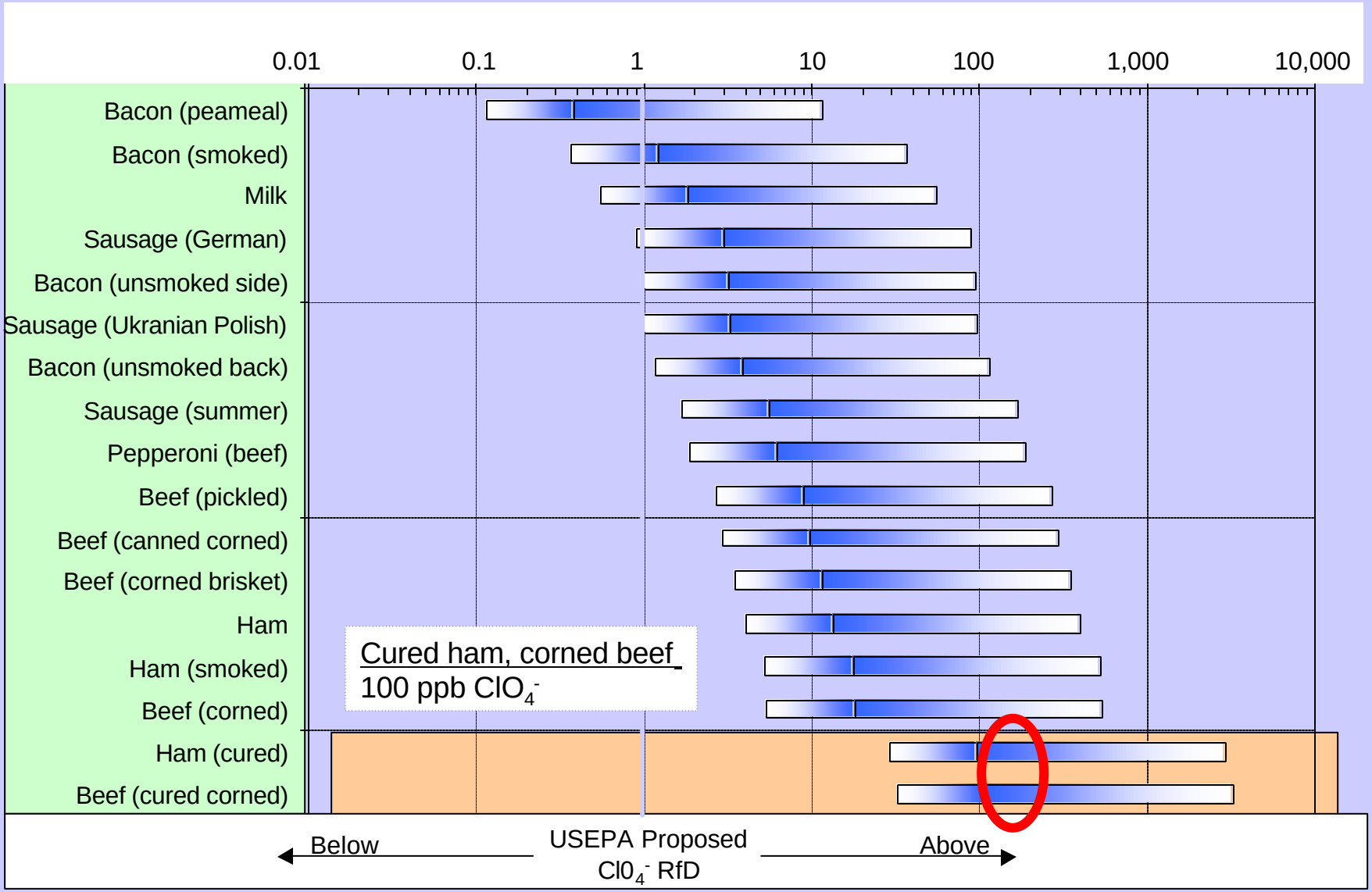
- **Same mechanism of action makes direct comparisons possible and highly relevant**
- **Much nitrate is found in common foods– especially green, leafy vegetables**
- **Nitrate in vegetables is normal**
- **These foods are considered safe and healthy**

Common foods containing nitrate

- ✓Milk
- ✓Bacon
- ✓Sausage
- ✓Pepperoni
- ✓Beef
- ✓Ham
- ✓Broccoli
- ✓Celery
- ✓Lettuce
- ✓Radish
- ✓Spinach
- ✓Beets
- ✓Rhubarb
- ✓Kimchi
- ✓Garlic
- ✓Artichoke
- ✓Peas
- ✓Corn
- ✓Sweet potatoes
- ✓Lima Beans
- ✓Cucumber
- ✓Tomatoes
- ✓Parsley
- ✓Brussels sprouts
- ✓White potatoes
- ✓Eggplant
- ✓Carrots
- ✓Onion
- ✓Green Beans
- ✓Melon
- ✓Turnip
- ✓Sweet pepper
- ✓Squash
- ✓Cabbage
- ✓Leek
- ✓Cauliflower
- ✓Pumpkin
- ✓Endive
- ✓Kale
- ✓Turnip Greens

IUI from Single Servings of Milk or Processed Meats Expressed in ppb of Perchlorate in Drinking Water

Best Professional Judgment Scenario Highlighted



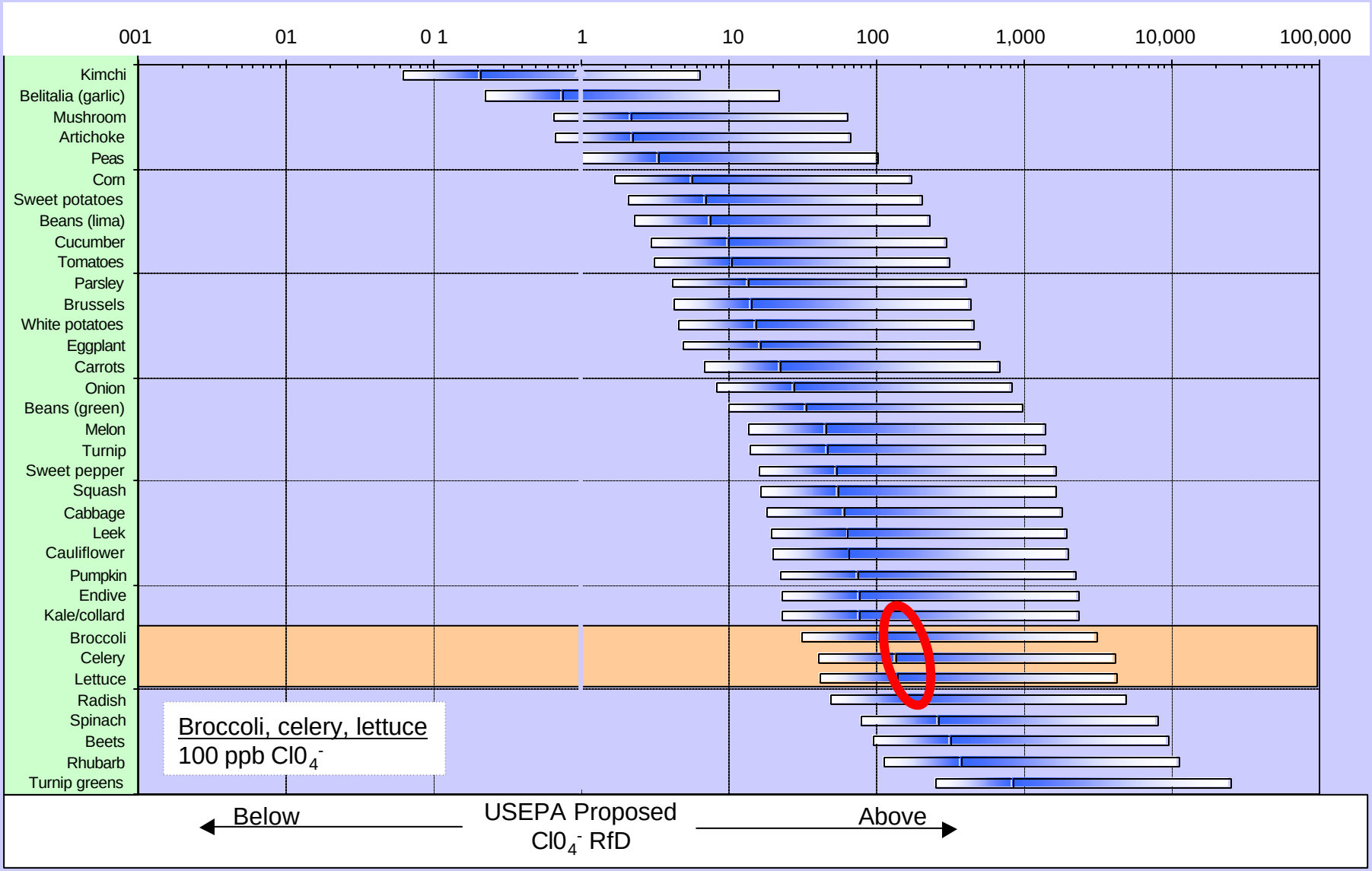
Broccoli Perchlorate Comparison

1/100th serving of broccoli = **2 liters of water with 1 ppb perchlorate**

=

IUI from Single Servings of Vegetables Expressed in ppb Perchlorate in Drinking Water

Best Professional Judgment Scenario Highlighted



Conclusions from comparative exposure assessment

- ***Iodide uptake inhibition*** **is common**
- **Compared to nitrate in our diet, perchlorate is a virtually nonexistent contributor to i*odide uptake inhibition***
- **<u>Single servings</u> of common foods have 10 to 1,000 times the *iodide uptake inhibition* potential as does perchlorate at EPA's proposed RfD/DWEL**
- ***Iodide uptake inhibition*** **from the total diet is likely to be hundreds or thousands of times greater**

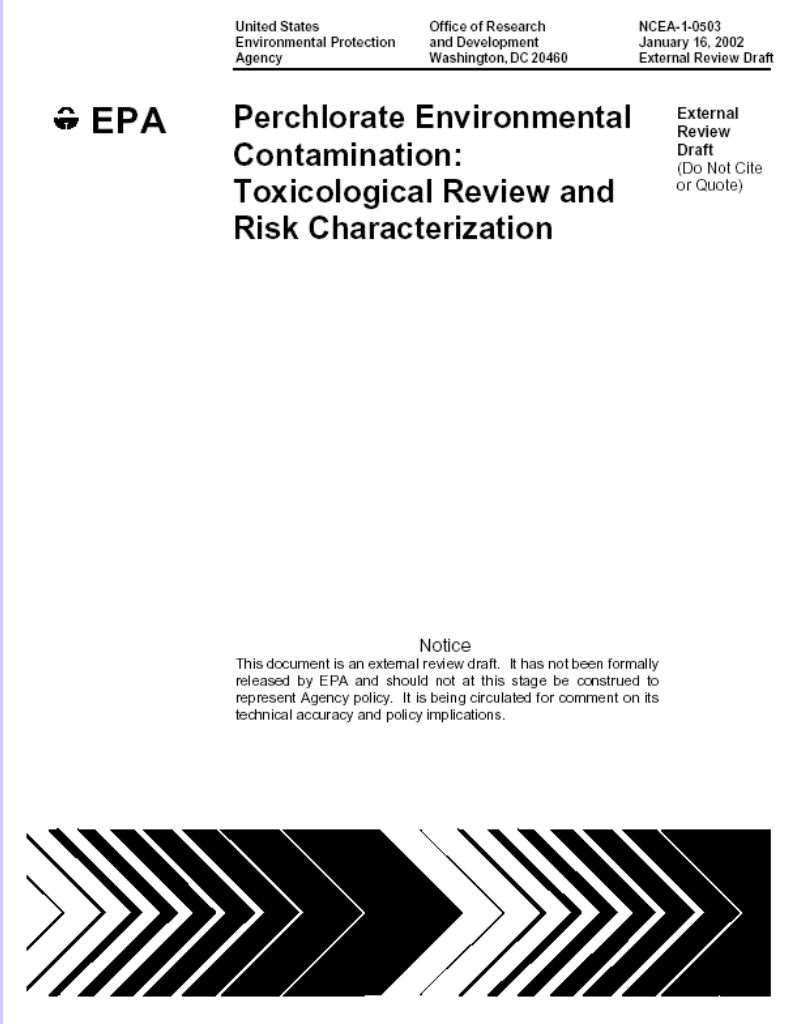
Implications if the science behind EPA's perchlorate risk assessment is right

- ***Iodide uptake inhibition*** **should be avoided**
- ***Iodide uptake inhibition*** **occurs well below 10,000 ppb nitrate**
- **Eating vegetables is much more dangerous than consuming perchlorate in drinking water**
- **The nitrate MCL is severely under-protective and needs to be reduced**
  - **To 300 ppb based on our judgment**
  - **Much lower if precaution guides decision**

Implications if the science behind EPA's nitrate risk assessment is right

- ***Iodide uptake inhibition*** **does <u>not</u> occur below 10,000 ppb**
- **Based on Greer *et al.* and comparative exposure assessment…**
  - ***Iodide uptake inhibition*** **occurs above 60 ppm nitrate**
  - **Consistent with the nitrate risk assessment choice of methemoglobinemia as the critical effect**
- **Science behind EPA's perchlorate risk assessment is not valid**

The EPA proposes an RfD/DWEL of 1 part per billion



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Alternative risk assessments in progress yield much higher values

Author	Based on	DWEL (ppb)
TERA	Greer *et al.*, 2002 20% IUI EPA std method	70
Pleus *et al.*, 2003	Greer *et al.*, 2002 study; based on no-effect level for IUI	200
Crump and Goodman, 2003	Greer *et al.*, 2002 reanalysis of data; geometric mean BMDL based on IUI EPA std alternative method	500

Conclusion

- EPA's proposed 1 ppb RfD/DWEL significantly understates how much perchlorate exposure is "safe"
- The true "safe" exposure level for perchlorate is much higher than EPA's proposed RfD
- An RfD as high as 200-500 ppb drinking water equivalent would be protective even for sensitive subpopulations

Acknowledgements

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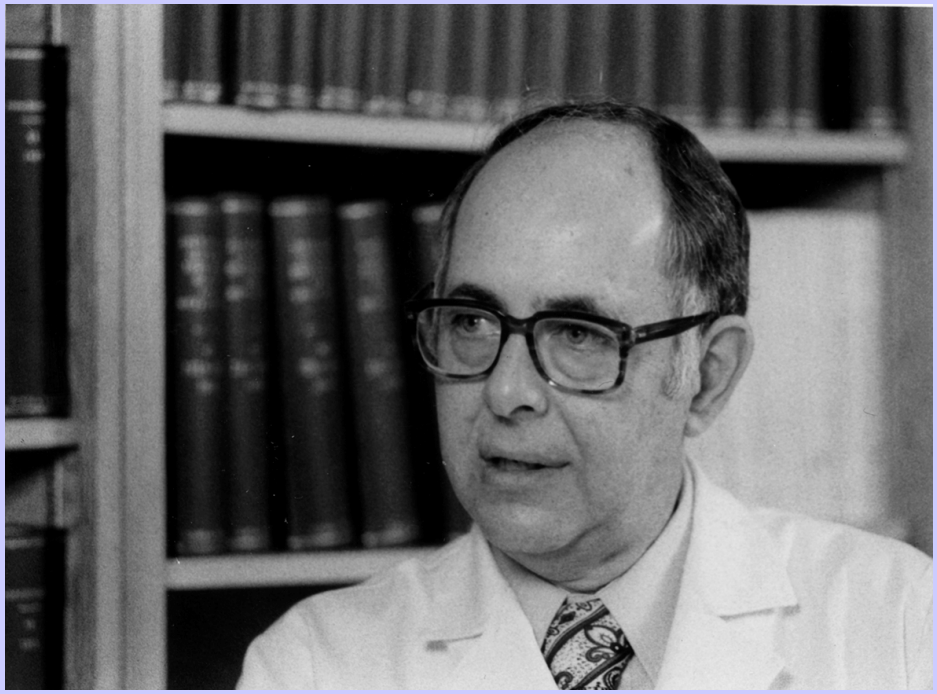

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Questions?

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